REMARKS

Applicants have amended the title to more specifically describe the invention. Submitted herewith is a response to the Notice to Comply, which amends the specification to include a copy of the sequence listing.

Applicants have cancelled Claims 9, 10 and 14-16 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

The claims have been amended to add the limitation that the claimed nucleic acids are more highly expressed in normal rectum compared to rectal tumor, or encode a polypeptide that is more highly expressed in normal rectum compared to rectal tumor. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification.

Claims 1-8 and 11-13 and 17-20 remain present for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed October 6, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Specification:

The PTO has objected to the title as not being descriptive. Applicants have amended the title herein.

The PTO has stated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The PTO states that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because the application does not contain, as a

separate part of the disclosure on a paper copy, a Sequence Listing as required by 37 C.F.R. § 1.821(c).

Applicants submit herewith a response to the Notice to Comply which amends the specification to include a paper copy of the Sequence Listing, which is also submitted herewith.

IDS:

The PTO has requested additional information on the references cited in the BLAST results reported in the Information Disclosure Statement filed September 12, 2002. Applicants submit herewith more detailed information regarding the publication date of the cited sequences (attached as Exhibit 1).

Priority Determination:

The PTO has stated that because no utility is disclosed in the priority applications, they are not enabling, thus no priority is granted. Priority under 35 U.S.C. § 120 is therefore set at the instant filing date, May 8, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 4, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/170262 filed 12/9/1999.

Applicants submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility. The sequences of SEQ ID NO:127 and SEQ ID NO:128 were first disclosed in US Provisional Application 60/170262 filed 12/9/1999 in Figures 1 and 2 and as SEQ ID NO:1 and SEQ ID NO:2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polynucleotides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Utility

The Office Action at page 3 states that the utility of the invention is based on the sequence identity of SEQ ID NO:128 to that of human alcohol dehydrogenase protein described by Meyers et al. Applicants assert that the claimed polynucleotides are useful as a diagnostic tool, based on the data that PRO1774 cDNA is more highly expressed in normal rectal tissue compared to rectal tumor.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO1774 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed nucleic acids. Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 2). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are

compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Regardless of whether the differential expression of the gene encoding PRO1774 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in normal rectum compared to rectal tumor, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 3). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide

expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 4) an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002) submitted herewith as Exhibit 5). Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Molecular Biology of the Cell at 302, emphasis added. Similarly, figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Molecular Biology of the Cell at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Molecular Biology of the Cell at 379.

Together, the declarations of Mr. Grimaldi and Dr. Polakis and the cited textbook establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1774 mRNA is expressed at a higher level in normal rectum compared to rectal tumor, the PRO1774 polypeptide will also be expressed at a higher level in normal rectum compared to rectal tumor. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed nucleic acids as a cancer diagnostic tool.

The Claimed Nucleic Acids would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1774, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 6, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 6), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith (attached as Exhibit 7). The article teaches that the HER-2/neu gene has been shown to

be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility, as would the nucleic acid which encodes it. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed nucleic acids.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1277 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the gene encoding the PRO1774 polypeptide is more highly expressed in normal rectum compared to rectal tumor. These data are strong evidence that gene encoding the PRO1774 polypeptide is associated with rectal tumors. Thus, Applicants submit that they have provided evidence associating the gene encoding the PRO1774 polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly rectal tumor, is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

Applicants have provided a declaration stating that the data in Example 18 reporting higher expression of the PRO1774 gene in normal rectal tissue compared to rectal tumor are real and significant. This declaration also indicates that given the relative difference in expression levels, the claimed nucleic acids have utility as cancer diagnostic tools. Applicants have also

shown that whether the differential expression of the PRO1774 gene is due to aneuploidy or not does not affect its usefulness as a diagnostic tool.

Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO1774 protein has utility as a diagnostic tool for cancer, and nucleic acids encoding the polypeptide also have utility as a result.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the gene encoding PRO1774 is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of nucleic acids.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as diagnostic agents. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids encoding PRO1774 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6, 8-10 and 14-20 under 35 U.S.C. § 112, second paragraph, as being indefinite.

The PTO objects to the phrase "the extracellular domain" as PRO1774 is not disclosed as being expressed on a cell surface. The PTO further objects to the recitation of "the extracellular

domain", "lacking its associated signal sequence" because a signal sequence is not generally considered part of an extracellular domain. Applicants have amended the claims to remove all references to "the extracellular domain."

The PTO also objects to the use of "hybridize" and "stringent conditions" since what hybridizes depends on the conditions under which the hybridization is carried out, and "stringent conditions" is a relative term. Applicants have cancelled Claims 14-16.

Thus, Applicants request that the PTO reconsider and withdraw the indefiniteness rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-5 and 14-20 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that, while the specification is enabling only for the polynucleotide of SEQ ID NO:127 or fragments of such that are usable as hybridization probes, it is not enabling for claims to polynucleotides with 80-99% sequence identity to SEQ ID NO:127, those which encode polypeptides with 80-99% sequence identity to SEQ ID NO:128, or those which hybridize to any of the above because there is no structural or functional information provided in the specification.

Applicants have amended the claims to incorporate the limitation that the claimed nucleic acids with less than 100% identity to SEQ ID NO:127, or which encode a protein with less than 100% identity to SEQ ID NO:128, must be more highly expressed in normal rectal tissue compared to rectal tumor, or encode a polypeptide that is more highly expressed in normal rectal tissue compared to rectal tumor. Applicants assert that techniques used to make variants of polynucleotide or polypeptide sequences are well-known to those of skill in the art (see, e.g., paragraph [0258] of the specification). Thus, the claims as amended contain sufficient structural information to enable the claims.

Applicants note that because they have established a utility for the PRO1774 polypeptide, supported by the declarations of experts in the field and several references, polynucleotides which encode the PRO1774 polypeptide also have utility. This includes degenerate polynucleotide sequences which encode the PRO1774 polypeptide. Therefore, contrary to the

PTO's assertion, polynucleotides that differ from SEQ ID NO:127 due to codon degeneracy are enabled.

While Applicants respectfully disagree that the hybridization claims are not enabled, these claims have been cancelled.

In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected Claims 1-5 and 14-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed polynucleotides encode a particular protein, or that any encoded protein possess any particular biological activity, the claims fail the written description requirement.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of

his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the pending claims concerns nucleic acids having a specified sequence identity with the disclosed polynucleotide sequence of SEQ ID NO:127, or encoding a polypeptide with the specified polypeptide sequence of SEQ ID NO:128, and as amended, with the functional recitation: "wherein said isolated nucleic acid is more highly expressed in normal rectal tissue compared to rectal tumor, or wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in normal rectal tissue compared to rectal tumor". Other claims relate to nucleic acids which hybridize to nucleic acids of SEQ ID NO:127, or polynucleotides which encode a polypeptide of SEQ ID NO:128, under the specified stringent conditions. Based on the detailed description of the cloning and expression of variants of PRO1774 in the specification, the description of the differential tissue expression assay, the actual reduction to practice of sequences SEQ ID NOs:127 and 128, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO rejects Claims 1-10 and 13-20 as anticipated under 35 U.S.C. §102(b) by Meyers et al. (AAB84364, WO 01/4446, published June 2001). According to the PTO, Meyers et al. disclose nucleotides encoding the amino acid sequence of SEQ ID NO:128, and describes nucleotides capable of hybridizing to nucleotides encoding the polypeptide of SEQ ID NO:128 as well as the expression of nucleotides containing vectors with promoter sequences in bacterial hosts. Applicants respectfully traverse.

To be anticipated under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Applicants submit that the cited reference does not

anticipate any of the pending claims because the reference was not published more than one year prior to the date of the instant application for patent in the United States.

As noted above, the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/170262 filed 12/9/1999. The sequences of SEQ ID NOs:128 and 127 were first disclosed in US Provisional Application 60/170262 filed December 9, 1999 in Figures 1 and 2 and as SEQ ID NOs:1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), were first disclosed in PCT Application PCT/US00/23328 filed August 24, 2000, on page 93, line 3, through page 96, line 35.

Applicants demonstrated, by means of the disclosure in their provisional application filed **December 9, 1999**, that they were in possession of so much of the claimed invention, i.e. SEQ ID NOs:127 and 128, as disclosed in the Meyers et al. reference published June 2001. In addition, the data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution) were first disclosed in PCT Application PCT/US00/23328 filed **August 24, 2000**, on page 93, line 3, through page 96, line 35. Applicants submit that the disclosures are fully enabling, such that Applicants are entitled to the benefit of these earlier filing dates. Accordingly, the cited reference is not prior art under §102(b). Applicants therefore respectfully request that the rejection be withdrawn.

Claims 14-16 are rejected as anticipated under 35 U.S.C. §102(b) by Birren et al. (AC003042/c, published July 1998). According to the PTO, Birren et al. disclose nucleotides capable of hybridizing to nucleotides encoding the polypeptide of SEQ ID NO:128.

Claims 14-16 have been cancelled, thereby obviating the rejection.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Jan. 5, 2005

By: _____

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